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Original Contribution

Dietary Determinants of One-Carbon Metabolism and the Risk of Non-Hodgkin's Lymphoma: NCI-SEER Case-Control Study, 1998–2000

U. Lim[1], M. Schenk[2], L. E. Kelemen[3], S. Davis[4], W. Cozen[5], P. Hartge[6], M. H. Ward[6], and R. Stolzenberg-Solomon[1]

[1] Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD.
[2] Department of Family Medicine, Wayne State University, Karmanos Cancer Institute, Detroit, MI.
[3] Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, MN.
[4] Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, WA.
[5] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA.
[6] Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD.

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The role of dietary one-carbon determinants remains largely unexplored for non-Hodgkin's lymphoma (NHL). In a population-based case-control study of non-African-American adult (aged 20–74 years) women and men from four US Surveillance, Epidemiology, and End Results study centers (Detroit, Michigan; Iowa; Los Angeles, California; and Seattle, Washington; 1998–2000), the authors examined folate; vitamins B_2, B_6, and B_{12}; methionine; and a one-carbon antagonist, alcohol, in 425 incident NHL cases and 359 controls who completed a detailed food frequency questionnaire. Adjusted odds ratios and 95% confidence intervals were estimated by using unconditional logistic regression. Higher intake of one-carbon determinants from food was associated with a lower risk of NHL, but that for only vitamin B_6 (highest vs. lowest quartile: odds ratio = 0.57, 95% confidence interval: 0.34, 0.95; *p* trend = 0.01) and methionine (odds ratio = 0.49, 95% confidence interval: 0.31, 0.76; *p* trend = 0.002) reached statistical significance. Folate from food was inversely associated with diffuse subtype (odds ratio = 0.47, 95% confidence interval: 0.23, 0.94; *p* trend = 0.03). The authors found no association between total (food plus supplement) vitamins and NHL. Nonusers of alcohol had an elevated NHL risk compared with users, and alcohol did not modify other nutrient-NHL associations. Findings suggest that one-carbon nutrients, particularly vitamin B_6 and methionine, may be protective against NHL.

alcohol drinking; case-control studies; folic acid; lymphoma, non-Hodgkin; methionine; riboflavin; vitamin B_6; vitamin B_{12}

Abbreviations: CI, confidence interval; NHL, non-Hodgkin's lymphoma; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results.

One-carbon metabolism refers to intracellular single-carbon transfer reactions (1). Folate, a B vitamin, serves as a one-carbon carrier and donates the one-carbon unit for methionine synthesis and subsequently for methylation of numerous compounds such as DNA (figure 1) (1). Methylation of DNA constitutes a major epigenetic mechanism by which genes are selectively activated (2). Folate also supplies one-carbon units for the synthesis of purines and

Correspondence to Dr. R. Stolzenberg-Solomon, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, EPS 320, Rockville, MD 20852 (e-mail: stolzenr@mail.nih.gov).

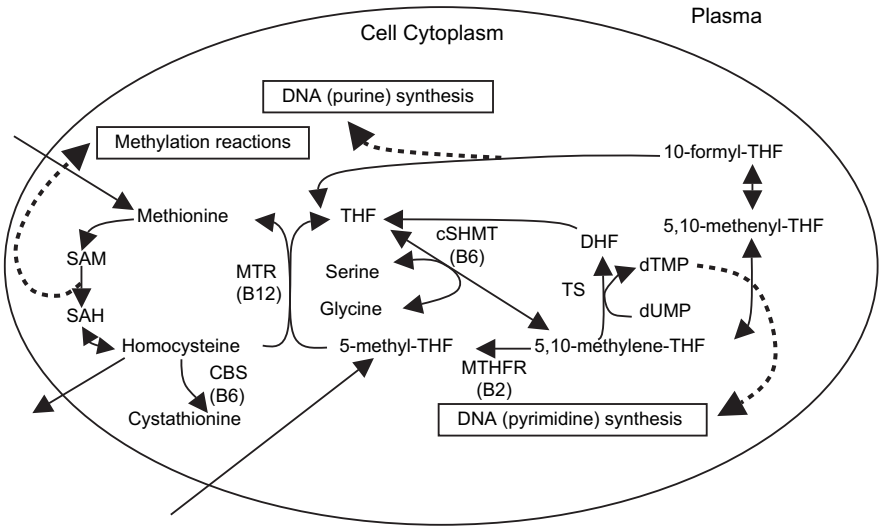

FIGURE 1. Diagram showing intracellular one-carbon metabolism and how nutritional determinants are involved, NCI-SEER study, United States, 1998–2000 (modified from J Nutr 2002;132(8 suppl):2413S–2418S, published by the American Society for Nutritional Sciences, with written permission from the journal and from Drs. Choi and Mason). B2, vitamin B_2; B6, vitamin B_6; B12, vitamin B_{12}; CBS, cystathionine beta-synthase; cSHMT, cytoplasmic serine hydroxymethyltransferase; DHF, dihydrofolate; dTMP, deoxy-thymidine monophosphate; dUMP, deoxy-uridine monophosphate; MTHFR, 5,10-methylenetetrahydrofolate reductase; MTR, methionine synthase; SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine; THF, tetrahydrofolate; TS, thymidylate synthase.

thymidylates required for DNA synthesis and repair (1). One-carbon metabolism also involves other nutrients as enzymatic cofactors (vitamins B_2, B_6, and B_{12}) and as alternative suppliers of one-carbon units (methionine): it is disrupted by alcohol (3, 4).

Abnormal one-carbon metabolism has been proposed to be carcinogenic, in part mediated by chromosomal instability and altered DNA methylation patterns (1). Such alterations may also be lymphomagenic because it is well established that non-Hodgkin's lymphoma (NHL) is accompanied by tumor suppressor genes with impaired integrity and altered methylation (5). In an animal model, genetically altered DNA methylation resulted in malignant lymphoid tumors (6). Recent case-control studies of humans reported that genetic polymorphisms of certain one-carbon metabolizing enzymes are associated with lymphomas (7–11). Furthermore, abnormal lymphocyte morphology and compromised immune responses are observed with deficiencies of folate, vitamin B_{12}, and methionine (12, 13) and suggest a causal link between nutritional determinants of one-carbon metabolism and NHL.

To date, few epidemiologic studies of NHL have examined the role of specific one-carbon nutrients. One prospective study of US women reported a null association between dietary folate and NHL (14). A number of epidemiologic studies have examined food groups that supply a large proportion of one-carbon nutrients in the United States (15), but the evidence for an association with NHL is inconsistent. Breads, grains, and ready-to-eat cereals (16–21) that provide folate and vitamins B_2 and B_6 yielded positive (17), inverse (16, 18, 22), or null (19, 21) associations with NHL. Vegetables (14, 17, 18, 20, 21, 23) and fruits (17, 20, 22, 24), natural sources of folate and vitamin B_6, showed inverse associations with NHL despite null findings for some food items (14, 16, 18, 21–23, 25). Dairy products containing methionine and vitamins B_2, B_{12}, and B_6 showed either positive (16, 18, 20, 21, 26) or null (17, 19, 22, 23, 25) associations. Animal protein from foods high in methionine and vitamins B_{12}, B_6, and B_2 exhibited null (17, 19) or positive (20–22) findings. The alcohol-NHL association is controversial, with mixed reports of positive (27, 28), negative (23, 29–33), and null (16, 18, 25, 34–37) associations. To our knowledge, the potential modification of the association between one-carbon nutrition and NHL by alcohol, as in the breast (38) and colorectum (4), has not been examined in relation to NHL. Given the lack of direct and consistent epidemiologic evidence, we conducted a US population-based case-control study to evaluate the hypothesis that a diet high in one-carbon determinants and low in alcohol may be inversely associated with the risk of NHL.

MATERIALS AND METHODS

Study population

The NHL case-control study participants were recruited from four US regions served by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute: the Detroit, Michigan, metropolitan region; the state of Iowa; Los Angeles County, California; and the Seattle, Washington, metropolitan region. Each registry identified all resident women and men aged 20–74 years who had a first primary diagnosis of NHL during the period July 1, 1998, to June 30, 2000, primarily from

pathology reports collected from hospitals and private laboratories. All cases of NHL, including chronic lymphocytic leukemia, were histologically confirmed and were classified according to the *International Classification of Diseases for Oncology*, Second Edition (codes 9590–9595, 9670–9717, and 9823). Details on the study design and data collection are available elsewhere (39). In Iowa and Seattle, all consecutive cases were chosen. In Los Angeles and Detroit, African-American cases were oversampled to increase the power for analyses stratified by race. Population controls were identified among residents of the four SEER Program areas who were aged 20–74 years and were negative for human immunodeficiency virus by self-report. Both eligible cases and controls with a previous diagnosis of NHL, but not other malignancies, were excluded. Controls under age 65 years were identified from households contacted via random digit dialing. Controls aged 65–74 years were identified from Health Care Financing Administration (Medicare) files.

The study was approved by the human subjects review boards at all participating institutions. Written informed consent was obtained before interview during the home visit.

Approximately 2,248 eligible cases negative for human immunodeficiency virus were identified with either extranodal or nodal NHL, and 2,409 eligible controls were selected randomly and were matched to cases by SEER Program center, gender, race, and age (5-year categories). Of these subjects, 1,321 cases and 1,057 controls were interviewed (39). Response rates were highest among women and in Iowa for both cases and controls, and more follicular lymphoma cases than cases with other subtypes responded.

We used a split-sample design to investigate different etiologic risk factors in detail but, at the same time, limit overburdening participants with a large number of questions. Study participants were placed in either group A (all African-American and 50 percent of non-African-American participants) for detailed self/family medical history or group B (50 percent of non-African-American participants) for detailed diet/lifestyle history in addition to answering a core set of questions. Each participant in group B received a mailed questionnaire on demographic characteristics and detailed diet history. During a subsequent home visit, trained interviewers administered computer-assisted personal interviews on abbreviated medical and family history, sunlight exposures, cell phone use, allergies, and hobbies. Of the eligible 905 cases and 978 controls in group B, respectively, 125 and 12 died before we could conduct the interview, four and nine moved out of the area, 45 and 116 were not locatable otherwise, and, for 30 cases, their physicians refused participation. Of the remaining 701 cases (77 percent) and 841 controls (86 percent) whom we approached, 552 cases (79 percent) and 462 controls (55 percent) were interviewed: subjects were not interviewed because they declined (99 cases, 311 controls) or never responded because of illness (14 cases, 13 controls), impairment (10 cases, 33 controls), or other reasons (26 cases, 22 controls). Of those approached overall, 484 cases (69 percent), mostly within 14 months after their diagnosis, and 419 controls (50 percent) returned the questionnaires.

Dietary assessment

Dietary intake was assessed by using a modified version of the self-administered Block 1995 revision of the Health Habits and History Questionnaire (40, 41). Its food list and the nutrient values were developed by using adults' dietary data from the Second National Health and Nutrition Examination Survey. The instrument included queries on 107 food and beverage items for responses on nine frequencies and three portion sizes, with reference medium portion sizes provided. Its 14 dietary supplement questions covered inquiries on dose, frequency, and duration of use of single and multivitamin supplements. The instrument was validated against multiple diet records (correlations for most nutrients were in the 0.5–0.6 range) (40, 42) and recently performed comparably to two other commonly used food frequency questionnaires in reference to more reliable 24-hour recall (43). For the current study, the written instruction of the questionnaire asked participants to answer the questions on the basis of ''usual eating habits, as an adult, before 1 year ago and not including any recent dietary changes.'' The scanned data from the 1995 version were further updated with values for vitamin B_{12} and methionine and with imputed estimates for postfortification-level folate, using the 1998 version of the Block database (http://www.nutritionquest.com/index.htm).

Statistical analyses

Of 484 cases and 419 controls who returned the questionnaire, 18 cases (10 women and eight men) and 28 controls (10 women and 18 men) were excluded because their responses had one of the following limitations: consumption of fewer than three foods (women) or fewer than four foods (men) per day, consumption of more than 30 foods per day, or more than 20 percent skipped responses. Additionally, 41 cases and 32 controls were excluded because they did not provide information on anthropometry or leisure-time physical activity, leaving 425 cases and 359 controls in the analyses.

Statistical analyses were conducted by using the SAS software system (version 8; SAS Institute, Inc., Cary, North Carolina). In this paper, all p values are two sided and were considered statistically significant at an alpha level of <0.05. Descriptive characteristics of cases and controls were compared by the Wilcoxon nonparametric test of continuous variables and by chi-squared tests of categorical variables (table 1). All food and nutrient variables were adjusted for energy intake by the nutrient density method: each nutrient variable was divided by daily energy intake for descriptive and regression analyses (44). B vitamins of study interest were examined as intake from food sources alone or combined with supplements. Unconditional logistic regression was used to estimate odds ratios and 95 percent confidence intervals for each nutrient-NHL association in simple and multivariable-adjusted regression models (table 2). Energy adjustment for all foods and nutrients was made by simultaneous inclusion in the regression model of the nutrient density variable and a variable for daily energy intake (44). Dietary variables, including energy-adjusted food and nutrients, were examined as both continuous and quartile variables categorized on the basis of the distribution among the

TABLE 1. Descriptive characteristics† of non-Hodgkin's lymphoma cases and controls who completed a food frequency questionnaire, NCI-SEER study, United States, 1998–2000

Characteristic	Cases ($n = 425$)	Controls ($n = 359$)
Sex: female	46	50
Age at diagnosis or selection (years)	57** (12)	60 (11)
20–34	6	3
35–44	13	8
45–54	21	16
55–64	28	25
65–74	33**	48
Race		
White	95	96
Other non–African American and unknown	5	4
Study center		
Detroit, Michigan	11	11
Iowa	37	36
Los Angeles, California	22	21
Seattle, Washington	29	32
Education		
<12 years	7	9
12–15 years	61	56
≥16 years	32	35
Body mass index (weight (kg)/height (m)^2)	27 (5.7)	27 (6.1)
Height (inches)‡	67.6 (4.0)	67.2 (3.9)
Smoking status		
Never	46	45
Ever	53	54
Current	18	15
Former	35	39
Total leisure-time exercise (metabolic equivalents/week)	637 (623)	660 (599)
Energy intake (kcal/day)	1,931** (760)	1,805 (703)
% from fat	36.7* (6.8)	35.4 (7.8)
% from protein	16.7** (3.0)	17.4 (3.2)
% from carbohydrate	46.0 (7.2)	45.9 (8.6)
Alcohol intake (g/week)	38.2** (88.8)	47.0 (91.9)
Never	52**	41
Ever	48**	59
Average intake among drinkers (g/week)	79.1 (114.5)	79.6 (108.2)
One-carbon nutrients§		
Folate (μg/1,000 kcal)		
Prefortification, from food¶	156** (51)	170 (62)
Prefortification, total¶	259 (149)	281 (161)
Vitamin B_{12} (μg/1,000 kcal)		
From food	2.2* (0.7)	2.3 (0.7)
Total	3.8 (2.1)	4.0 (2.2)
Vitamin B_6 (mg/1,000 kcal)		
From food	0.9** (0.2)	1.0 (0.3)
Total	1.5 (0.7)	1.5 (0.8)
Vitamin B_2 (mg/1,000 kcal)		
From food	1.06* (0.30)	1.11 (0.33)
Total	1.4* (0.6)	1.5 (0.6)
Methionine (g/1,000 kcal)	0.9** (0.2)	1.0 (0.2)
Multivitamin supplements	49	47
Other nutrients§		
Vitamin C (mg/1,000 kcal)	54** (28)	58 (29)
Dietary fiber (g/1,000 kcal)	7.6 (2.7)	7.9 (3.1)

* $p < 0.05$; ** $p \leq 0.01$ for comparison of cases with controls using the Wilcoxon nonparametric test for continuous variables and the Pearson chi-squared test for categorical variables.

† Values are presented as mean (standard deviation) for continuous variables or percentage for categorical variables.

‡ One inch = 2.54 cm.

§ Nutrient and food variables were adjusted for total energy intake by the nutrient density method.

¶ Postfortification folate levels showed results similar to those for prefortification folate: compared with controls, cases had lower food folate but similar total folate intake.

controls. Alcohol intake was categorized as nondrinkers and drinkers of tertile doses. Since alcohol intake was moderately correlated with total energy intake ($r = 0.20$, $p < 0.001$), its association with NHL was determined both without and with energy adjustment because the latter is known to reduce the impact of measurement error on risk estimates (45). We examined both pre- and postfortification levels of folate but present the analysis of prefortification folate in this paper because chronic dietary exposure before the recruitment period is more relevant than the current intake status affected by fortification since 1998.

A linear trend of the association between a categorical nutrient and NHL was determined by the two-sided Wald test of a score variable that contained median nutrient values of the categories. Effect modification of each nutrient-NHL association by risk factors, including demographic, lifestyle, and other nutritional factors, was evaluated by including a score variable of the nutrient, the risk factor, and their product term in the adjusted models. Effect modification was considered statistically significant for p values of <0.10 of the cross-product term and by a significant likelihood ratio test statistic from the comparison of models with and without the product term. The associations of one-carbon nutrients with each main NHL subtype were obtained in multivariable-adjusted polytomous logistic regression

models (table 3). Heterogeneity of the nutrient-NHL subtype associations was tested by case-only analysis of diffuse versus follicular subtypes (46).

Each nutrient-NHL association was examined in separate regression models. Simple adjusted models included daily energy intake and the four frequency-matching factors: age (<35, 35–44, 45–54, 55–64, ≥65 years), gender, race (White, non-African-American others and unknown combined), and study center (Detroit, Iowa, Los Angeles, Seattle). Each nutrient-NHL model was built from the simple adjusted model by including potential confounding risk factors one at a time. Variables were considered confounders if they were associated with both the nutrient of interest and NHL in descriptive analyses and if they changed the risk estimate of the nutrient-NHL association by 10 percent or more. The final multivariable models were additionally adjusted for education (<12 years, 12–15 years, ≥16 years), body mass index (weight in kilograms/height in meters squared); 20–25 as referent, <20, 25–30, >30), leisure-time exercise expressed in metabolic equivalents per week (0 for no exercise, 30–270, 271–675, 676–1,080, >1,080), smoking status (never, former, current), dietary fiber from grain products (energy-adjusted quartiles), alcohol (categories of none and tertiles of weekly intake in grams), and methionine (energy-adjusted quartiles).

RESULTS

Table 1 presents selected descriptive characteristics of the 425 cases and 359 controls for whom complete diet and covariate information was available. Cases and controls were similar with respect to education, body mass index, height, smoking exposure, and extent of leisure-time exercise, but cases had higher intakes of total energy, a greater percentage of calories from fat, and a smaller percentage of calories from protein. Cases also consumed less alcohol and less one-carbon nutrients from food sources, including folate; vitamins B_{12}, B_6, and B_2; and methionine. Use of multivitamin supplements and total (food plus supplement) B-vitamin intake were similar in cases and controls except for total vitamin B_2, which was lower in cases. Compared with controls, cases also had lower vitamin C but similar total fiber intake.

Table 2 shows the simple and multivariable-adjusted odds ratios and 95 percent confidence intervals for the association between each nutritional determinant of one-carbon metabolism and NHL. Compared with subjects in the lowest category, those in the highest category had lower odds ratios of NHL; however, those for only vitamin B_6 (odds ratio (OR) = 0.57, 95 percent confidence interval (CI): 0.34, 0.95; p trend = 0.01) and methionine (OR = 0.49, 95 percent CI: 0.31, 0.76; p trend = 0.002) reached statistical significance. The analysis using postfortification levels of folate in food yielded a similar association as using prefortification folate (data not shown).

About half of the participants (49 percent of cases and 47 percent of controls) took multivitamin supplements that included the four B vitamins (table 1). Regular use of multivitamins was categorized into less than one and one tablet of standard multivitamin supplements per day, which corresponded to the most common unit amount of each B vitamin taken from supplements alone (footnote, table 2). Contrary to the results for B-vitamin intake from food sources, neither B-vitamin intake from supplements alone nor total B-vitamin intake was associated with NHL risk (table 2). In an extended analysis, we found that more cases (20 percent) than controls (11 percent) had started using the multivitamin supplements in recent years—less than 3 years before the study. When recent use was treated as a separate category, it was associated with a significantly elevated risk of NHL (OR = 1.76, 95 percent CI: 1.12, 2.77) compared with no use. Similarly, the risk estimates for total vitamins among long-term users were closer to the estimates for food vitamins; for example, for total vitamin B_6, the multivariable odds ratios for higher quartiles were 0.99, 0.86, and 0.77 (95 percent CI: 0.46, 1.30; p trend = 0.3).

Nonusers of alcohol had a significantly elevated NHL risk compared with users. Nondrinking was associated with about an 80 percent increased risk of NHL compared with drinking (OR = 1.79 comparing nondrinkers with all drinkers, 95 percent CI: 1.30, 2.47). Estimates for alcohol adjusted for energy showed similar results (data not shown). None of the associations between one-carbon nutrients and NHL was significantly modified by alcohol intake, multivitamin use, or other one-carbon nutrients, and there was no interaction among folate, vitamin B_6, methionine, and alcohol (all p for interaction > 0.10; data not shown).

Adjusting for fiber from grains strengthened the association of folate and vitamin B_6 with NHL. An adjustment for methionine attenuated the association between vitamin B_{12} and NHL substantially and the associations of vitamins B_2 and B_6 with NHL to a lesser degree. Other potential confounders that did not change the risk estimates included family history, farmer status, smoking duration (years, pack-years) and intensity, and intake of food vitamin C, vegetables, fruits, red meats, fat (total, saturated, or animal), and dairy products (data not shown).

The nutrient-NHL associations were examined for the major NHL subtypes by using polytomous logistic regression (table 3). Diffuse lymphomas (36 percent) were the most common histologic subtype identified, followed by follicular (25 percent). T-cell lymphoma was uncommon (5 percent), and odds ratio estimates were not determined because of the small numbers. Food folate and vitamin B_6 each showed a stronger inverse association with diffuse than with follicular lymphoma, but only folate results were statistically significantly different for the two subtypes (p for heterogeneity = 0.02). The associations for methionine and alcohol remained similar with follicular and diffuse subtypes. B-vitamin intake from supplements alone or total B vitamins was not associated significantly with either subtype.

DISCUSSION

We found inverse associations between one-carbon nutrients and NHL, particularly for food vitamin B_6 and methionine. Food folate did not show a significant association with all NHL types combined but was inversely associated with the diffuse subtype. Nondrinking was associated with an increased risk of NHL as compared with drinking and did not modify other nutrient-NHL associations.

TABLE 2. Multivariable-adjusted association of individual dietary one-carbon determinants with non-Hodgkin's lymphoma, NCI-SEER study, United States, 1998–2000

	Cases ($n = 425$)	Controls ($n = 359$)	Simple adjusted*		Multivariable adjusted†	
			OR‡	95% CI‡	OR	95% CI
Folate (μg/1,000 kcal)						
From food						
<124	126	89	1.00	Referent	1.00	Referent
124 to <161	123	94	1.02	0.69, 1.51	1.02	0.67, 1.55
161 to <202	97	89	0.89	0.59, 1.34	0.90	0.57, 1.43
≥202	79	87	0.74	0.48, 1.13	0.73	0.44, 1.21
p trend			0.1		0.2	
Total						
<146	115	90	1.00	Referent	1.00	Referent
146 to 238	119	89	1.13	0.76, 1.69	1.31	0.85, 2.02
>238 to 396	106	93	0.96	0.64, 1.43	1.05	0.68, 1.63
≥396	85	87	1.00	0.64, 1.56	1.17	0.72, 1.90
p trend			0.7		0.9	
Vitamin B_{12} (μg/1,000 kcal)						
From food						
<1.87	131	92	1.00	Referent	1.00	Referent
1.87 to <2.29	117	91	0.90	0.61, 1.32	0.90	0.58, 1.39
2.29 to <2.75	101	87	0.86	0.57, 1.28	1.02	0.63, 1.65
≥2.75	76	89	0.64	0.42, 0.97	0.84	0.49, 1.45
p trend			0.04		0.6	
Total						
<2.22	128	90	1.00	Referent	1.00	Referent
2.22 to <3.31	101	89	0.81	0.54, 1.21	0.90	0.58, 1.39
3.31 to <5.58	105	94	0.77	0.51, 1.14	0.85	0.56, 1.30
≥5.58	91	86	0.95	0.62, 1.45	1.13	0.70, 1.80
p trend			0.8		0.6	
Vitamin B_6 (mg/1,000 kcal)						
From food						
<0.81	125	91	1.00	Referent	1.00	Referent
0.81 to <0.97	136	89	1.20	0.81, 1.77	1.22	0.80, 1.87
0.97 to <1.12	99	89	0.90	0.60, 1.35	0.94	0.59, 1.49
≥1.12	65	90	0.57	0.37, 0.88	0.57	0.34, 0.95
p trend			0.005		0.01	
Total						
<0.92	124	91	1.00	Referent	1.00	Referent
0.92 to <1.30	108	89	0.92	0.62, 1.38	1.02	0.66, 1.56
1.30 to <2.14	115	91	0.94	0.64, 1.39	1.02	0.67, 1.54
≥2.14	78	88	0.80	0.51, 1.23	0.90	0.56, 1.46
p trend			0.4		0.7	

Table continues

The only known prior study of NHL on specific one-carbon nutrients addressed folate and found no significant association (14). In the prospective investigation of 199 incident NHL cases during a 14-year follow-up of 88,410 female nurses, neither folate from foods nor total folate intake was associated with NHL when women in the highest quintile (median folate intake of 379 μg/day from food or 698 μg/day in total) were compared with women in the lowest quintile (median intake of 151 μg/day from food or 158 μg/day in total). The overall null association for folate and the distribution of folate intake among our female participants are consistent with this previous study (14).

TABLE 2. Continued

	Cases ($n = 425$)	Controls ($n = 359$)	Simple adjusted*		Multivariable adjusted†	
			OR	95% CI	OR	95% CI
Vitamin B_2 (mg/1,000 kcal)						
From food						
<0.88	131	92	1.00	Referent	1.00	Referent
0.88 to <1.07	105	88	0.86	0.58, 1.28	0.83	0.54, 1.27
1.07 to <1.29	106	91	0.87	0.58, 1.29	0.88	0.58, 1.36
≥1.29	83	88	0.72	0.48, 1.09	0.81	0.50, 1.30
p trend			0.1		0.4	
Total						
<1.02	125	89	1.00	Referent	1.00	Referent
1.02 to <1.44	121	90	0.99	0.67, 1.46	0.99	0.66, 1.50
1.44 to <1.96	92	93	0.76	0.51, 1.14	0.81	0.52, 1.25
≥1.96	87	87	0.88	0.58, 1.35	0.97	0.60, 1.55
p trend			0.3		0.7	
Methionine from food (g/1,000 kcal)						
<0.84	129	91	1.00	Referent	1.00	Referent
0.84 to <0.97	121	89	0.98	0.67, 1.45	0.83	0.55, 1.25
0.97 to <1.09	107	88	0.88	0.59, 1.31	0.78	0.51, 1.18
≥1.09	68	91	0.56	0.37, 0.86	0.49	0.31, 0.76
p trend			0.01		0.002	
Multivitamin supplement§						
As reported						
None	218	189	1.00	Referent	1.00	Referent
<1/day	58	35	1.35	0.84, 2.16	1.47	0.89, 2.40
≥1/day	149	135	1.07	0.78, 1.46	1.11	0.80, 1.55
p trend			0.6		0.5	
Recent use (<3 years) separately¶						
None	218	189	1.00	Referent	1.00	Referent
Any <3 years	78	39	1.67	1.08, 2.59	1.76	1.12, 2.77
Any ≥3 years						
<1/day	23	23	0.84	0.45, 1.57	0.92	0.48, 1.75
≥1/day	86	104	0.81	0.57, 1.16	0.84	0.57, 1.23
Alcohol intake (g/week)						
None	220	147	1.85	1.22, 2.79	1.71	1.12, 2.61
<18	70	71	1.00	Referent	1.00	Referent
18–70	67	70	0.83	0.50, 1.37	0.86	0.52, 1.44
>70	68	71	1.06	0.65, 1.73	0.99	0.59, 1.66

* Adjusted for age, gender, race (Whites vs. non-African-American others and unknown), study center (Detroit, Michigan; Iowa; Los Angeles, California; Seattle, Washington), and total energy intake.

† Additionally adjusted for education, body mass index, leisure-time physical activity, smoking status, fiber intake from grains, alcohol intake, and methionine intake.

‡ OR, odds ratio; CI, confidence interval.

§ One multivitamin supplement per day corresponded to 400 μg of folic acid, 6 μg of vitamin B_{12}, 2 mg of vitamin B_6, and 2 mg of vitamin B_2.

¶ The number of subjects is reduced to those who reported the duration of their supplement use: 405 cases and 355 controls.

To our knowledge, this investigation is the first to report a significant inverse association of vitamin B_6 or methionine with the risk of NHL. However, the inverse association between vitamin B_6 and NHL was limited to food sources and was not confirmed for total vitamin B_6 that includes multivitamin supplements. In fact, we observed general attenuation of the nutrient-NHL associations for all four B vitamins when supplemental intake was included. Under

TABLE 3. Multivariable-adjusted association of dietary one-carbon determinants with non-Hodgkin's lymphoma subtypes,* NCI-SEER study, United States, 1998–2000

	Follicular lymphoma ($n = 107$)			Diffuse lymphoma ($n = 153$)			Other/unknown lymphoma ($n = 142$)		
	No.	OR†,‡	95% CI†	No.	OR‡	95% CI	No.	OR‡	95% CI
Folate (μg/1,000 kcal)									
From food									
<124	26	1.00	Referent	53	1.00	Referent	40	1.00	Referent
124 to <161	28	1.24	0.64, 2.42	47	0.89	0.52, 1.53	39	0.96	0.54, 1.68
161 to <202	23	1.14	0.54, 2.39	30	0.65	0.35, 1.20	41	1.08	0.60, 1.97
≥202	30	1.76	0.82, 3.78	23	0.47	0.23, 0.94	22	0.57	0.28, 1.16
p trend		0.3			0.03			0.2	
Total									
<146	23	1.00	Referent	43	1.00	Referent	42	1.00	Referent
146 to <238	28	1.66	0.83, 3.33	47	1.43	0.81, 2.52	39	1.10	0.62, 1.94
238 to <396	31	1.57	0.79, 3.12	41	1.14	0.64, 2.01	28	0.73	0.40, 1.34
≥396	25	2.05	0.95, 4.46	22	0.90	0.45, 1.81	33	1.03	0.54, 1.94
p trend		0.2			0.9			0.6	
Vitamin B_{12} (μg/1,000 kcal)									
From food									
<1.87	34	1.00	Referent	51	1.00	Referent	37	1.00	Referent
1.87 to <2.29	32	0.86	0.44, 1.67	40	0.70	0.39, 1.26	37	1.20	0.65, 2.20
2.29 to <2.75	22	0.72	0.34, 1.52	40	0.99	0.53, 1.85	37	1.50	0.78, 2.90
≥2.75	19	0.58	0.25, 1.36	22	0.60	0.28, 1.27	31	1.40	0.66, 2.94
p trend		0.2			0.5			0.3	
Total									
<2.22	30	1.00	Referent	50	1.00	Referent	38	1.00	Referent
2.22 to <3.31	24	0.85	0.43, 1.68	33	0.68	0.38, 1.22	41	1.35	0.75, 2.42
3.31 to <5.58	23	0.77	0.39, 1.50	47	0.96	0.56, 1.66	29	0.81	0.44, 1.49
≥5.58	30	1.59	0.79, 3.23	23	0.76	0.39, 1.48	34	1.34	0.71, 2.52
p trend		0.5			0.9			0.9	
Vitamin B_6 (mg/1,000 kcal)									
From food									
<0.81	34	1.00	Referent	44	1.00	Referent	38	1.00	Referent
0.81 to <0.97	27	0.97	0.51, 1.87	56	1.36	0.78, 2.37	48	1.29	0.73, 2.28
0.97 to <1.12	21	0.80	0.39, 1.62	35	0.99	0.53, 1.84	37	0.98	0.53, 1.81
≥1.12	25	0.89	0.42, 1.87	18	0.46	0.22, 0.96	19	0.48	0.23, 0.99
p trend		0.5			0.06			0.03	

Table continues

the proposed hypothesis, any protective effect of one-carbon nutrients against NHL is expected to be stronger when data for persons whose intake from supplements is higher are incorporated, especially considering the higher bioavailability of some of the vitamins in supplements compared with food (47, 48). It is possible, but unlikely, that yet-unidentified confounding factors would have explained the inconsistency regarding all four vitamins.

Alternatively, the reported supplemental vitamins may not represent long-term intake in this retrospective assessment of past diet. For example, NHL patients might have modified certain health-related behaviors in recent years because of experiencing subclinical symptoms or as a post-diagnosis regimen, including recent initiation of supplement use, which would have driven the true underlying relation in the direction of a positive association between supplemented nutrients and NHL. In support of our speculation, more cases than controls had started taking supplements in recent years, and total vitamin intake appeared more inversely associated with NHL among long-term supplement users.

Latent disease progression or postdiagnosis behavior modification should be considered in the interpretation of current findings. Our study had low response rates, although similar to the recent generation of population-based

TABLE 3. Continued

	Follicular lymphoma ($n = 107$)			Diffuse lymphoma ($n = 153$)			Other/unknown lymphoma ($n = 142$)		
	No.	OR‡	95% CI	No.	OR‡	95% CI	No.	OR‡	95% CI
Total									
<0.92	25	1.00	Referent	49	1.00	Referent	41	1.00	Referent
0.92 to <1.30	27	1.36	0.69, 2.67	40	0.98	0.56, 1.72	38	1.01	0.57, 1.79
1.30 to <2.14	31	1.44	0.75, 2.78	45	1.02	0.59, 1.75	32	0.80	0.45, 1.43
≥2.14	24	1.47	0.69, 3.12	19	0.64	0.32, 1.28	31	0.94	0.50, 1.77
p trend		0.4			0.6			0.6	
Vitamin B_2 (mg/1,000 kcal)									
From food									
<0.88	34	1.00	Referent	48	1.00	Referent	39	1.00	Referent
0.88 to <1.07	27	0.84	0.44, 1.61	32	0.64	0.36, 1.14	39	1.03	0.58, 1.81
1.07 to <1.29	25	0.76	0.39, 1.47	43	1.02	0.58, 1.79	38	1.03	0.57, 1.84
≥1.29	21	0.67	0.32, 1.41	30	0.87	0.46, 1.64	26	0.80	0.42, 1.55
p trend		0.2			0.8			0.5	
Total									
<1.02	25	1.00	Referent	47	1.00	Referent	44	1.00	Referent
1.02 to <1.44	33	1.42	0.74, 2.70	44	0.97	0.56, 1.66	40	0.91	0.52, 1.57
1.44 to <1.96	23	0.95	0.47, 1.91	40	1.02	0.58, 1.80	23	0.53	0.29, 0.99
≤1.96	26	1.47	0.70, 3.08	22	0.72	0.37, 1.42	35	0.98	0.53, 1.81
p trend		0.9			0.8			0.5	
Methionine from food (g/1,000 kcal)									
<0.84	31	1.00	Referent	47	1.00	Referent	41	1.00	Referent
0.84 to <0.97	32	0.97	0.52, 1.82	47	0.83	0.48, 1.42	36	0.84	0.47, 1.47
0.97 to <1.09	29	0.99	0.52, 1.87	36	0.68	0.38, 1.19	37	0.91	0.52, 1.61
≥1.09	15	0.44	0.21, 0.94	23	0.42	0.23, 0.79	28	0.68	0.37, 1.24
p trend		0.06			0.004			0.3	
Multivitamin supplement									
None	49	1.00	Referent	79	1.00	Referent	77	1.00	Referent
<1/day	16	1.78	0.86, 3.69	25	1.71	0.92, 3.19	15	1.16	0.58, 2.31
≥1/day	42	1.45	0.87, 2.43	49	1.05	0.67, 1.65	50	0.99	0.64, 1.55
p trend		0.2			0.5			0.9	
Alcohol intake (g/week)									
None	61	2.53	1.23, 5.19	76	1.43	0.82, 2.50	69	1.47	0.82, 2.63
<18	12	1.00	Referent	31	1.00	Referent	25	1.00	Referent
18–70	18	1.17	0.50, 2.76	26	0.76	0.38, 1.51	19	0.76	0.37, 1.57
>70	16	1.19	0.50, 2.85	20	0.69	0.34, 1.38	29	1.23	0.62, 2.45

* There were too few T-cell lymphoma cases ($n = 23$) to analyze.

† OR, odds ratio; CI, confidence interval.

‡ Multivariable odds ratios were adjusted for age, gender, race (Whites vs. non-African-American others and unknown), study center (Detroit, Michigan; Iowa; Los Angeles, California; Seattle, Washington), total energy intake, education, body mass index, leisure-time physical activity, smoking status, fiber intake from grains, alcohol intake, and methionine intake.

case-control studies that included home visits. We used three strategies to assess whether the responders differed from nonresponders and how this might have impacted our results. We repeated the analyses in Iowa or among women, the subgroups with the highest response rates, and found similar results, except for the following differences: the association was attenuated for vitamin B_6 in Iowa (multivariable-adjusted OR comparing the highest with the lowest quartile = 0.94, 95 percent CI: 0.35, 2.50) and for alcohol intake among women (adjusted OR comparing nondrinkers with drinkers of <18 g/week = 1.51, 95 percent CI: 0.85, 2.67). Secondly, since we observed a slight overrepresentation of high/middle socioeconomic status, including education, among responders compared with nonresponders in an

ancillary study of the Los Angeles area, we stratified our analysis by educational level and did not find deviations from the overall estimates. These observations, added to the fact that there was no confounding by study center, gender, or education, indicate that the impact of the low participation rates is likely to be minor.

Strengths of our study include ascertainment of cases through multiple SEER Program registries across the country and selection of population-based controls, which might have made our findings more generalizable over convenience-sampled case-control data. We used a validated food frequency questionnaire, which allowed for adjustment of energy intake and other dietary factors that could have confounded the associations of interest.

Our observation of the inverse associations of vitamin B_6 and methionine with NHL is biologically plausible. Vitamin B_6 bound to the folate-regulating enzyme, cytoplasmic serine hydroxymethyltransferase, appears to inhibit subunit exchanges of the enzyme's tetramer structure and therefore stabilize the enzyme (figure 1) (49). Genetic polymorphisms of cytoplasmic serine hydroxymethyltransferase are associated with an altered risk of lymphoma (8) and adult acute lymphocytic leukemia (50) potentially because they interfere with the enzyme's modulation of its critical substrate, 5,10-methylenetetrahydrofolate, between DNA synthesis and methylation pathways (51). Vitamin B_6 is also a structural and functional component of cystathionine beta-synthase (52). Deficiency and genetic variants, and possibly lack of the vitamin cofactor, of cystathionine beta-synthase can elevate homocysteine and subsequently *S*-adenosylhomocysteine through reversible conversion (53), which in turn would inhibit methylation reactions through a negative feedback (54).

Similarly, methionine intake may be protective against lymphomagenesis by supplying *S*-adenosylmethionine and, thereafter, DNA methylation reactions through the irreversible conversions of *S*-adenosylmethionine to *S*-adenosylhomocysteine. Methionine deficiency has induced liver cancer in animals (55) and may be tumorigenic also in lymphoid cells with high turnover rates (12). Total protein, an important source of vitamin B_6 and methionine, was also inversely associated with NHL in these data (A. Cross, National Cancer Institute, personal communication, 2004). Although vitamins B_{12} and B_2 are key players in one-carbon metabolism, we did not find any associations with NHL, possibly because of the adequate intake by study participants on the US diet in reference to the Dietary Reference Intake recommendations (table 1) (56).

Contrary to our hypothesis of an antagonistic effect of alcohol on one-carbon metabolism, the associations between one-carbon nutrients and NHL were similar for drinkers and nondrinkers. No use of alcohol was positively associated with NHL in our data, with a threshold type of pattern. Others have reported similarly elevated NHL risk among nondrinkers (29, 33), although the mechanisms that may explain such associations are unclear. Previous studies and our case-control studies may be subject to reverse causation and/or differential recall, particularly if a proportion of NHL cases became nondrinkers as a result of not feeling well and because cases may systematically underreport their past alcohol intake, respectively (57), which is supported by the lack of dose response.

The nonsignificant inverse association we observed between food folate and overall NHL was stronger and significant for the diffuse subtype. The inverse associations of food vitamin B_6 and methionine showed a stronger trend with diffuse than follicular subtype as well. A recent large case-control study of diet and NHL in Canada reported significant heterogeneity across NHL subtypes (21). We are unaware of any biologic mechanism by which the potentially protective effect of one-carbon metabolism may vary by NHL subtypes. Nevertheless, our finding is intriguing considering heterogeneous etiologic mechanisms (58), demographic makeup, and incidence trends (59) proposed for different subtypes of NHL.

Our study points to the need for further investigation of one-carbon nutrition, alcohol intake, and NHL as well as alcohol's interaction with one-carbon nutrients in pooled case-control studies and prospective cohort studies to determine the association for subtypes of NHL with more precision and to eliminate the possible influence of recall bias in the retrospective design. Our findings represent the associations of one-carbon nutrients with NHL before the era of folate fortification of the US food supply. Whether and how the impact and dynamics of one-carbon nutrients might have changed with the fortification needs to be determined. In addition, consideration of gene-nutrient interaction may clarify the specific associations for the at-risk group that may have different nutritional demands than the rest of the population.

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